Wyeth-Ayerst Laboratories—Cont.

DRUG/LABORATORY TEST INTERACTIONS
The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:
Pregnancy Tests
Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.
Glucose Tolerance Test
An increase in blood glucose has been reported in patients receiving promethazine.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.
PREGNANCY
Teratogenic Effects —Pregnancy Category C
Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women. Phenergan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects
Promethazine taken within two weeks of delivery may inhibit platelet aggregation in the newborn.
LABOR AND DELIVERY
Phenergan, in appropriate dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See "Indications and Usage" and "Dosage and Administration.")
See also "Nonteratogenic Effects."
NURSING MOTHERS
It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.
PEDIATRIC USE
This product should not be used in children under 2 years of age because safety for such use has not been established.

ADVERSE REACTIONS

Nervous System —Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).
Cardiovascular —Increased or decreased blood pressure.
Dermatologic —Rash, rarely photosensitivity.
Hematologic —Rarely leukopenia, thrombocytopenia; agranulocytosis (1 case).
Gastrointestinal —Nausea and vomiting.

OVERDOSAGE

Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.
Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares.
Atropinelike signs and symptoms—dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms, may occur.
TREATMENT
Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature, and EKG need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine are not reversed by naloxone. Avoid analeptics which may cause convulsions.
Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure.
Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

ALLERGY
The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Children tolerate this product well. Single 25-mg doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms.
Phenergan Rectal Suppositories may be used if the oral route is not feasible, but oral therapy should be resumed as soon as possible if continued therapy is indicated.
The administration of promethazine hydrochloride in 25-mg doses will control minor transfusion reactions of an allergic nature.
MOTION SICKNESS
The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, Phenergan Tablets, Syrup, or Rectal Suppositories, 12.5 to 25 mg, twice daily, may be administered.
NAUSEA AND VOMITING
The average effective dose of Phenergan for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (cf. Phenergan Injection) or by rectal suppository. 12.5- to 25-mg doses may be repeated, as necessary, at 4- to 6-hour intervals.
For nausea and vomiting in children, the usual dose is 0.5 mg per pound of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.
For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4- to 6-hour intervals, as necessary.
SEDATION
This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg Phenergan by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.
PRE- AND POSTOPERATIVE USE
Phenergan in 12.5- to 25-mg doses for children and 50-mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.
For preoperative medication children require doses of 0.5 mg per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropinelike drug.
Usual adult dosage is 50 mg Phenergan with an equal amount of meperidine and the required amount of a belladonna alkaloid.
Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5 to 25 mg in children and 25- to 50-mg doses in adults.
Phenergan Syrup Plain and Phenergan Syrup Fortis are not recommended for children under 2 years of age.

HOW SUPPLIED

Phenergan® (Promethazine Hydrochloride) Syrup Plain is a clear, green solution supplied as follows:
NDC 0008-0549-02, case of 24 bottles of 4 fl. oz. (118 mL).
NDC 0008-0549-03, bottle of 1 pint (473 mL).
Phenergan® (Promethazine Hydrochloride) Syrup Fortis is a clear, light straw-colored solution supplied as follows:
NDC 0008-0231-01, bottle of 1 pint (473 mL).
Keep bottles tightly closed.
Store at Room Temperature, between 15° C and 25° C (59° F and 77° F).
Protect from light.
Dispense in light-resistant, glass, tight containers.

PHENERGAN® R

[fen'er-gan]
(promethazine HCl)
TABLETS •
SUPPOSITORIES

DESCRIPTION

Each tablet of Phenergan contains 12.5 mg, 25 mg, or 50 mg promethazine hydrochloride. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength also contains the following:
12.5 mg—FD&C Yellow 6 and saccharin sodium;
25 mg—saccharin sodium;
50 mg—FD&C Red 40.
Each rectal suppository of Phenergan contains 12.5 mg, 25 mg, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter.
Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88.
Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as N,N,α-trimethyl-10H-phenothiazine-10-ethanamine monohydrochloride.
Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

CLINICAL PHARMACOLOGY

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopaminergic (CNS) action.
Promethazine is an H_1 receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative and antiemetic effects. In therapeutic dosage, promethazine produces no significant effects on the cardiovascular system.
Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

INDICATIONS AND USAGE

Phenergan, either orally or by suppository, is useful for:
Perennial and seasonal allergic rhinitis.
Vasomotor rhinitis.
Allergic conjunctivitis due to inhalant allergens and foods.
Mild, uncomplicated allergic skin manifestations of urticaria and angioedema.
Amelioration of allergic reactions to blood or plasma.
Dermographism.
Anaphylactic reactions, as adjunctive therapy to epinephrine and other standard measures, after the acute manifestations have been controlled.
Preoperative, postoperative, or obstetric sedation.
Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery.
Therapy adjunctive to meperidine or other analgesics for control of postoperative pain.
Sedation in both children and adults, as well as relief of apprehension and production of light sleep from which the patient can be easily aroused.
Active and prophylactic treatment of motion sickness.
Antiemetic therapy in postoperative patients.

CONTRAINDICATIONS

Promethazine is contraindicated in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines.
Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

WARNINGS

Promethazine may cause marked drowsiness. Ambulatory patients should be cautioned against such activities as driving or operating dangerous machinery until it is known that they do not become drowsy or dizzy from promethazine therapy.
The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, narcotic analgesics, sedatives, hypnotics, and tranquilizers should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half, and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.
Promethazine may lower seizure threshold. This should be taken into consideration when administering to persons with known seizure disorders or when giving in combination with narcotics and local anesthetics which may also affect seizure threshold.
Sedative drugs or CNS depressants should be avoided in patients with a history of sleep apnea.
Antihistamines should be used with caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.
Administration of promethazine has been associated with reported cholestatic jaundice.

PRECAUTIONS

GENERAL

Promethazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

INFORMATION FOR PATIENTS

Phenergan may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. Ambulatory patients should be told to avoid engaging in such activities until it is known that they do not become drowsy or dizzy from Phenergan therapy. Children should be supervised to avoid potential harm in bike riding or in other hazardous activities.

The concomitant use of alcohol or other central nervous system depressants, including narcotic analgesics, sedatives, hypnotics, and tranquilizers, may have an additive effect and should be avoided or their dosage reduced.

Patients should be advised to report any involuntary muscle movements or unusual sensitivity to sunlight.

DRUG INTERACTIONS

The sedative action of promethazine is additive to the sedative effects of other central nervous system depressants, including alcohol, narcotic analgesics, sedatives, hypnotics, tricyclic antidepressants, and tranquilizers; therefore, these agents should be avoided or administered in reduced dosage to patients receiving promethazine.

DRUG/LABORATORY TEST INTERACTIONS

The following laboratory tests may be affected in patients who are receiving therapy with promethazine hydrochloride:

Pregnancy Tests

Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations.

Glucose Tolerance Test

An increase in blood glucose has been reported in patients receiving promethazine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to assess the carcinogenic potential of promethazine, nor are there other animal or human data concerning carcinogenicity, mutagenicity, or impairment of fertility with this drug. Promethazine was nonmutagenic in the *Salmonella* test system of Ames.

PREGNANCY

Teratogenic Effects —Pregnancy Category C

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine. These doses are from approximately 2.1 to 4.2 times the maximum recommended total daily dose of promethazine for a 50-kg subject, depending upon the indication for which the drug is prescribed. Specific studies to test the action of the drug on parturition, lactation, and development of the animal neonate were not done, but a general preliminary study in rats indicated no effect on these parameters. Although antihistamines, including promethazine, have been found to produce fetal mortality in rodents, the pharmacological effects of histamine in the rodent do not parallel those in man. There are no adequate and well-controlled studies of promethazine in pregnant women. Phenergan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Promethazine taken within two weeks of delivery may inhibit platelet aggregation in the newborn.

LABOR AND DELIVERY

Phenergan, in appropriate dosage form, may be used alone or as an adjunct to narcotic analgesics during labor and delivery. (See "Indications and Usage" and "Dosage and Administration.")

See also "Nonteratogenic Effects."

NURSING MOTHERS

It is not known whether promethazine is excreted in human milk. Caution should be exercised when promethazine is administered to a nursing woman.

PEDIATRIC USE

This product should not be used in children under 2 years of age because safety for such use has not been established.

ADVERSE REACTIONS

Nervous System —Sedation, sleepiness, occasional blurred vision, dryness of mouth, dizziness; rarely confusion, disorientation, and extrapyramidal symptoms such as oculogyric crisis, torticollis, and tongue protrusion (usually in association with parenteral injection or excessive dosage).

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Dermatologic —Rash, rarely photosensitivity.

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Gastrointestinal —Nausea and vomiting.

OVERDOSAGE

Signs and symptoms of overdosage with promethazine range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, and unconsciousness.

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Atropine-like signs and symptoms—dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms, may occur.

TREATMENT

Treatment of overdosage is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs, including respiration, pulse, blood pressure, temperature, and EKG, need to be monitored. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine are not reversed by naloxone. Avoid analeptics which may cause convulsions.

Severe hypotension usually responds to the administration of norepinephrine or phenylephrine. EPINEPHRINE SHOULD NOT BE USED, since its use in patients with partial adrenergic blockade may further lower the blood pressure.

Limited experience with dialysis indicates that it is not helpful.

DOSAGE AND ADMINISTRATION

ALLERGY

The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Children tolerate this product well. Single 25-mg doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms. The administration of promethazine hydrochloride in 25-mg doses will control minor transfusion reactions of an allergic nature.

MOTION SICKNESS

The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal. For children, Phenergan Tablets, Syrup, or Rectal Suppositories, 12.5 to 25 mg, twice daily, may be administered.

NAUSEA AND VOMITING

The average effective dose of Phenergan for the active therapy of nausea and vomiting in children or adults is 25 mg. When oral medication cannot be tolerated, the dose should be given parenterally (cf. Phenergan Injection) or by rectal suppository. 12.5- to 25-mg doses may be repeated, as necessary, at 4- to 6-hour intervals.

For nausea and vomiting in children, the usual dose is 0.5 mg per pound of body weight, and the dose should be adjusted to the age and weight of the patient and the severity of the condition being treated.

For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, the average dose is 25 mg repeated at 4- to 6-hour intervals, as necessary.

SEDATION

This product relieves apprehension and induces a quiet sleep from which the patient can be easily aroused. Administration of 12.5 to 25 mg Phenergan by the oral route or by rectal suppository at bedtime will provide sedation in children. Adults usually require 25 to 50 mg for nighttime, presurgical, or obstetrical sedation.

PRE- AND POSTOPERATIVE USE

Phenergan in 12.5- to 25-mg doses for children and 50-mg doses for adults the night before surgery relieves apprehension and produces a quiet sleep.

For preoperative medication children require doses of 0.5 mg per pound of body weight in combination with an equal dose of meperidine and the appropriate dose of an atropine-like drug.

Usual adult dosage is 50 mg Phenergan with an equal amount of meperidine and the required amount of a belladonna alkaloid.

Postoperative sedation and adjunctive use with analgesics may be obtained by the administration of 12.5 to 25 mg in children and 25- to 50-mg doses in adults.

Phenergan Tablets and Phenergan Rectal Suppositories are not recommended for children under 2 years of age.

HOW SUPPLIED

Phenergan® (promethazine HCl) Tablets are available as follows:

12.5 mg, orange tablet with "WYETH" on one side and "19" on the scored reverse side.
NDC 0008-0019-01, bottle of 100 tablets.

25 mg, white tablet with "WYETH" and "27" on one side and scored on the reverse side.
NDC 0008-0027-02, bottle of 100 tablets.
NDC 0008-0027-07, Redipak® carton of 100 tablets (10 blister strips of 10).

50 mg, pink tablet with "WYETH" on one side and "227" on the other side.
NDC 0008-0227-01, bottle of 100 tablets.

Keep tightly closed.
Store at room temperature, between 15°C and 25°C (59°F and 77°F).
Protect from light.
Dispense in light-resistant, tight container.
Use carton to protect contents from light.

Phenergan® (promethazine HCl) Rectal Suppositories are available in boxes of 12 as follows:

12.5 mg, ivory, torpedo-shaped suppository wrapped in copper-colored foil, NDC 0008-0498-01.
25 mg, ivory, torpedo-shaped suppository wrapped in light-green foil, NDC 0008-0212-01.
50 mg, ivory, torpedo-shaped suppository wrapped in blue foil, NDC 0008-0229-01.

Store refrigerated between 2°–8°C (36°–46°F).
Dispense in well-closed container.

Shown in Product Identification Guide, page 340

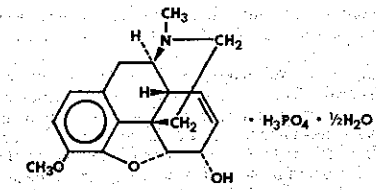
PHENERGAN® ℞

[*fen'er-gan*]
with codeine
(Warning—may be habit-forming)
(Promethazine Hydrochloride and Codeine Phosphate) Syrup

DESCRIPTION

Each teaspoon (5 mL) of Phenergan with codeine contains 10 mg codeine phosphate (Warning—may be habit-forming) and 6.25 mg promethazine hydrochloride in a flavored syrup base with a pH between 4.7 and 5.2. Alcohol 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C Red 33, FD&C Blue 1, FD&C Yellow 6, glycerine, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

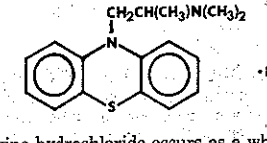
Codeine is one of the naturally occurring phenanthrene alkaloids of opium derived from the opium poppy; it is classified pharmacologically as a narcotic analgesic. Codeine phosphate may be chemically named as (5α,6α)-7,8-didehydro-4, 5-epoxy-3-methoxy-17-methylmorphinan-6-ol phosphate (1:1) (salt) hemihydrate with the following structural formula:



The phosphate salt of codeine occurs as white, needle-shaped crystals or white crystalline powder. Codeine phosphate is freely soluble in water and slightly soluble in alcohol, with a molecular weight of 406.37. The empirical formula is $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$, and the stereochemistry is 5α, 6α isomer as indicated in the structure.

Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \cdot HCl$ and its molecular weight is 320.88.

Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as N,N,α-trimethyl-10*H*-phenothiazine-10-ethanamine monohydrochloride with the following structural formula:



Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

CLINICAL PHARMACOLOGY

CODEINE

Narcotic analgesics, including codeine, exert their primary effects on the central nervous system and gastrointestinal tract. The analgesic effects of codeine are due to its central action; however, the precise sites of action have not been

Continued on next page